Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

By the above amendments, claims 1 and 12 are amended. No new matter is entered. Claims 1, 5, 8, 9, 12, 19, 20, and 27 are pending.

The rejection of claims 1, 5, 8, 9, 12, 19, 20, and 27 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments to the claims.

The rejection of claims 1, 8, 9, 12, 19, and 20 under 35 U.S.C. § 102(b) as anticipated by WO 99/27944 to Schenk ("Schenk") or, in the alternative, under 35 U.S.C. § 103(a) for obviousness over Schenk in view of Soto et al., "Alzheimer's *β*-Amyloid Peptide is Conformationally Modified by Apolipoprotein E *In Vitro*," *NeuroReport* 7:721-725 (1996) ("Soto I"), and U.S. Patent 5,948,763 to Soto-Jara et al. ("Soto-Jara") is respectfully traversed.

The claims of the present application are directed to methods that involve administering to a subject an agent, where the agent (1) is a protein comprising an amino acid sequence of at least 5 of the amino acids, in sequence, of SEQ ID NO:3, the protein including residue 7 of SEQ ID NO:3 and having an amino acid substitution of the valine at residue 7 which renders the protein non-fibrillogenic, and (2) inhibits interaction between amyloid-β peptide and apolipoprotein E, compared to when the agent is absent.

Schenk teaches compositions and methods for treatment of amyloidogenic diseases. The methods involve administering an agent that induces a beneficial immune response against an amyloid deposit in the patient. The methods are said to be particularly useful for prophylactic and therapeutic treatment of Alzheimer's disease. In such methods, a suitable agent is Aβ peptide or a variant or fragment thereof, or an Aβ peptide antibody.

Soto I teaches that apoE promotes Aβ fibrillogenesis by inducing a conformational change from a random coil or α-helix to a β-sheet structure in Aβ incorporated into amyloid. It is suggested that Alzheimer's Aβ-fibrillogenesis is conformationally modulated by apoE and that this protein is acting as a pathological chaperone promoting the transition between the non-amyloidogenic and amyloidogenic Aβ conformers.

Soto-Jara relates to peptides and pharmaceutical compositions for the treatment of disorders associated with abnormal protein folding into amyloid deposits. This reference teaches that substitution of the hydrophilic residues for hydrophobic ones in the internal Aβ hydrophobic regions (amino acids 17-21) impairs fibril formation. A particular inhibitory peptide is the five amino acid fragment LPFFD.

In making this rejection, the U.S. Patent and Trademark Office ("PTO") has taken the position that since Schenk teaches treatment of Alzheimer's disease by administration of amyloid β peptides of different length, substitutions, and modification, "the instant claimed method is fully encompassed and anticipated by Schenk even though Schenk . . . does not specifically recite the particular embodiments of the instant invention." According to the PTO, Schenk describes a genus of amyloid peptides that is relatively limited due to the length of the amyloid peptide itself, so that the fragments and substituted species are easily envisaged by one of ordinary skill in the art.

The problem with the PTO's position is that Schenk describes agents (*i.e.*, an Aβ peptide or a variant or fragment thereof) that are said to *induce a beneficial immune response* against an amyloid deposit in the patient, whereas the methods of the present application are directed to administering an agent (having a specific structure not taught by Schenk) that *inhibits interaction between amyloid-β peptide and apolipoprotein E*. As described in the present application at ¶ [0083], the agents of the present claims (*e.g.*, Aβ12-28p) were tested for immune response and it was concluded that, unlike the agents of Schenk, the effect of the agents of the present invention *cannot be attributed to a humoral response* against Aβ. Thus, the agents of the present invention have a completely different function compared to the agents of Schenk. This functional difference can be accounted for by structural differences in the amino acid sequences of the agents. *See e.g.,* present application, ¶ [0010] (a fibrillogenic and toxic Aβ peptide is rendered non-fibrillogenic and non-toxic by a single amino acid substitution).

Thus, contrary to the assertions of the PTO, a person of ordinary skill in the art, when considering Schenk, would not have envisaged the agents administered in the claimed methods of the present application, because the claimed agents have been modified structurally from anything disclosed in Schenk to achieve a different function. If anything, Schenk would have taught away from the claimed methods of the present application, because this reference teaches the selection of Aβ peptides having a structure that would

cause them to induce an immune response, as opposed to inhibiting the interaction between amyloid-β peptide and apolipoprotein E, as required by the present claims.

The PTO further points to Soto-Jara and Soto et al., "β-Sheet Breaker Peptides Inhibit Fibrillogenesis in a Rat Brain Model of Amyloidosis: Implications for Alzheimer's Therapy," *Nat. Med.* 4:822-826 (1998) ("Soto II"), for specifically describing the significance of the 17-20 region of Aβ and proline substitutions within this region. Soto II, like Soto-Jara, teaches that the central hydrophobic region in the N-terminal domain of Aβ, amino acids 17-20, serve as a template for designing the β-sheet breaker peptide *i*Aβ5 (LPFFD). Amino acid substitutions in this region of Aβ are said to produce large changes in the peptide's conformation and its ability to make amyloid fibrils. *i*Aβ5 was shown to inhibit, in a dose-dependent manner, amyloid formation by Aβ1-40 and Aβ1-42 *in vitro*. In view of the teachings of these references, the PTO asserts that the amyloid peptides covered by the present invention can be easily envisaged by one of ordinary skill in the art and recognized within a relatively low genus of amyloid peptides disclosed by Schenk. Applicants respectfully disagree.

Neither Soto II nor Soto-Jara (or any other reference cited by the PTO in the office action) teach or suggest an agent comprising an amino acid sequence of at least 5 of the amino acids, in sequence, of SEQ ID NO:3, where the protein includes residue 7 of SEQ ID NO:3 and has an amino acid substitution of the valine at residue 7, as claimed. One of the agents disclosed in Soto II and Soto-Jara (LPFF**D**) is structurally similar to (but still different from) an agent encompassed by the present claims (*e.g.*, the Aβ peptide fragment LPFF**A**). However, the agents disclosed in Soto II and Soto-Jara are said to inhibit Aβ fibrillogenesis (*see* Soto-Jara, Figure 12 and Soto II, p. 822 (*i*Aβ5 is a β-sheet breaker)), whereas the agents of the present invention target the pathomechanism of Alzheimer's disease (*i.e.*, ApoE/Aβ interaction), and are therefore distinguishable from agents that inhibit Aβ fibrillogenesis. *See* present application, ¶ [0005]. Accordingly, the agents disclosed in Soto II and Soto-Jara require a structure distinct from that of the agents of the present invention (*e.g.*, an amino acid substitution at both residue 7 *and residue 10 (i.e., A→D)* of SEQ ID NO:3) to achieve their distinct function of inhibiting Aβ fibrillogenesis.

Thus, if anything, Soto II and Soto-Jara teach away from the methods of the presently claimed invention, because they teach agents that differ in structure from the agents of the present invention and this difference in structure accounts for a difference in activity of

the agents compared to the agents recited in the claims of the present application. Soto I does not overcome these deficiencies.

For all of these reasons, the rejection based on Schenk, Soto I, and Soto-Jara is improper and should be withdrawn.

In view of all of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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/Tate L. Tischner/
Tate L. Tischner
Registration No. 56,048

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1363
Facsimile: (585) 263-1600